DIVISION OF PULMONARY, ALLERGY, and RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	April 22, 2010
To:	Michael Adjodha, DAGID, CDRH
From:	Brian Oscar Porter, M.D., Ph.D., M.P.H., Medical Reviewer
Through:	Susan Limb, M.D., Medical Team Leader
Through:	Badrul Chowdhury, M.D., Ph.D., Division Director
Subject:	Mercury allergy and dental amalgam

Brian Oscar Porter 4/26/10

4/26/10

for Badrul Chowdhury 4/26/10

General Information

NDA/IND#:	Not applicable
Sponsor:	Not applicable
Product:	Dental amalgam (mercury-based dental fillings)
Request From:	Michael Adjodha (CDRH/ODE/DAGID/DDB)
Date of Request:	December 14, 2009
Date Received:	December 14, 2009
Requested Completion:	April 30, 2010
Materials Reviewed:	Citizen's Petitions for Reconsideration of Docket #FDA-2008-N-0163 from Turner (September 2, 2009) and Love-Reeves (September 3, 2009); Final Rule pursuant to 21 CFR Part 872 regarding dental amalgams (Federal Register: Vol.74, No. 148, August 4, 2009); FDA web materials: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171094.htm

Background

This is a Medical Officer review in response to an interagency consultation request from CDRH, Office of Device Evaluation (ODE)/Division of Anesthesiology, General Hospital, Infection Control, & Dental Devices (DAGID)/Dental Devices Branch (DDB) regarding allergic responses to mercury in dental amalgam used to fill caries or structural defects in teeth. A Final Rule regarding dental amalgams pursuant to 21 CFR Part 872 (Federal Register: Vol.74, No. 148, August 4, 2009) was recently issued (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171094.htm), and DPARP was previously consulted on this same issue (September 1, 2009).

The Final Rule contains the following statements regarding potential mercury allergy in relation to dental amalgam:

> "FDA concludes that existing data indicate that certain individuals with a pre-existing hypersensitivity or allergy to mercury may be at risk for adverse health effects from mercury vapor released from dental amalgam."
>
> "Dental amalgam is associated with a risk of adverse tissue reaction, particularly in individuals with a mercury allergy, who may experience additional allergic reactions."

In turn, the Final Rule recommends the following labeling language for mercury-containing dental amalgams:

> "Contraindication: Do not use in persons with known mercury allergy."

Following publication of the Final Rule, several Citizen Petitions for Reconsideration of Docket #FDA-2008-N-0163 were submitted to CDRH. DPARP has been requested to provide consultation in reference to the following petitions:

- Turner, J. Petition for Reconsideration of the Final Rule for Dental Amalgam; Submitted: September 2, 2009
- Love, J. & Reeves, R. Petition for Reconsideration of the Final Rule for Dental Amalgam; Submitted: September 3, 2009

The petitions raised multiple concerns over the FDA decision regarding dental amalgams, including several points related to potential allergic reactions to mercury. Thus, ODE/DAGID/DDB has requested input from DPARP in formulating a response to these concerns, particularly regarding the definition, diagnosis, and genetic predisposition to mercury allergy. The consultation request from ODE/DAGID/DDB did not include specific questions for DPARP to address; however, review of the respective petitions indicated that the petitions questioned the Agency's definition and recommendations for the clinical management of mercury allergy.

To assist in the development of a discussion of these issues, a PubMED search and review of the English-language literature on mercury allergy currently available through the National Library of Medicine were conducted. Peer-reviewed articles including individual case reports, case series, Letters to the Editor, original research articles, and topical reviews pertinent to the issues raised by the Citizen Petitions were identified using the following search methodology:

Step	Search Procedure	# of References
#1	Search **mercury AND allergy** Limits: **only items with abstracts, Humans, English**	**232**
#2	Search **diagnosis OR diagnostic OR screening** Limits: **only items with abstracts, Humans, English**	**3,096,397**
#3	Search **#1 AND #2** Limits: **only items with abstracts, Humans, English**	**146**

#4	Search **genetic OR predisposition** Limits: **only items with abstracts, Humans, English**	**417,991**
#5	Search **#1 AND #4** Limits: **only items with abstracts, Humans, English**	**18**
#6	Search **amalgam** Limits: **only items with abstracts, Humans, English**	**3,029**
#7	Search **#1 AND #6** Limits: **only items with abstracts, Humans, English**	**108**
#8	Search **#3 OR #5 OR #7** Limits: **only items with abstracts, Humans, English** Sort by: **Publication Date**	**193**
#9	**Selected 160 pertinent documents from #8** based on abstract review, excluding articles not considered pertinent to consult	**162**

Additional peer-reviewed references cited in the bibliographies of the references listed in Step #9, but which were not identified by this PubMED search, were individually reviewed as deemed necessary for the purposes of this consultation. Collectively, these articles constitute the primary reference source for this document and are selectively cited within the text of this consultation. Of note, 33 of the 193 manuscripts identified by the automated portion of this PubMED search (Step #8) were excluded from the review by manual screening, as abstracts indicated they would be uninformative for this consultation, given their primary focus on divergent topics, e.g., relationship of mercury exposure to non-allergic conditions such as autism, multiple sclerosis, infertility, and oral cancer; allergies to metals other than mercury; animal models of mercury-induced disease. Of note, the majority of manuscripts reviewed were generated by European investigators.

Responses to the questions raised by the Citizen Petitions are provided below:

Questions based on Citizen Petitions for Reconsideration submitted to CDRH:

1) What is mercury allergy and how common is it in the general population?

Division Response:
Mercury allergy denotes an immunologic hypersensitivity reaction to mercury in any of its chemical forms (pure metal particles or vapor, inorganic, organic, or salt formulations). Per the Gell & Coombs classification system for hypersensitivity reactions, mercury allergy typically takes the form of localized delayed-type cell-mediated cutaneous or mucosal reactions (reviewed in Holmstrup, 1991), although Type I IgE-mediated immediate hypersensitivity reactions such as burning or pruritic urticaria have occasionally been reported. By definition, immediate hypersensitivity reactions to mercury are acute and occur within several hours of exposure. However, progression to anaphylaxis has rarely been reported, although some case reports

describe the development of wheezing (Ilhan Kal, et al., 2008; Galindo, et al., 1997). Unlike with other types of IgE-mediated allergens such as certain foods and insect venoms, mortality and severe morbidity have not been reported due to mercury hypersensitivity. Rather, the more common form of delayed-type contact hypersensitivity to mercury is characterized by subacute, mild to moderate cutaneous and mucosal reactions, which develop over the course of several days following initial exposure (McGivern, et al., 2000). These reactions to mercury are due to the activation of allergen-specific T cells by antigen-presenting Langerhans cells, which induces inflammatory cytokine and chemokine production, leading to cytotoxic effects and the subsequent recruitment of additional leukocytes, including macrophages and eosinophils (Forte, et al., 2008; Laine, et al., 1999). These immune cells act in concert to amplify the inflammatory reaction, which typically manifests as a localized erythematous, eczematous, and pruritic skin lesion that may also be vesicular, ulcerated, or even pustular in its most severe form (Lerch & Bircher, 2004; Yiannias, et al., 1998; Roujeau, et al., 1991). Such reactions may be either self-limited or persistent, although they are not life-threatening, as neither Toxic Epidermal Necrolysis nor Stevens-Johnson Syndrome (SJS) has been associated with mercury exposure. Interestingly, a recent case report describes an episode of pediatric SJS in response to chelation therapy for chronic mercury exposure (Van der Linde, et al., 2008).

Overall, mercury allergy is a rare condition with no obvious risk factors. Although some case series have suggested females are disproportionately affected as compared to males, gender differences appear more striking with respect to mercury metabolism and potential toxicities (Vahter, et al., 2006). Limited evidence also suggests a negative correlation between mercury allergy and age, which may relate to the timing of mercury exposure (Wöhrl, et al., 2003; Brasch & Geier, 1997). The majority of allergic responses to mercury are thus localized contact reactions, as generalized hypersensitivity manifestations, such as distal cutaneous responses, are extremely rare (Fardal, et al., 2005; Ulukapi, 1995). Estimates of the prevalence of mercury allergy vary within the peer-reviewed literature, largely due to variable diagnostic criteria and inconsistencies in the operationalizing of mercury allergy and/or sensitivity, as several forms of mercury-associated reactions have been described. For example, a non-localized form of contact dermatitis known historically as "Baboon Syndrome" has been associated with systemic exposure to mercury (most commonly from broken liquid thermometers), which is characterized by the development of diffuse symmetric erythematous exanthema at distal body sites that form across large flexural surfaces, such as the medial thighs and buttocks, antecubital fossae, or anterolateral neck (Belhadjali, et al., 2008; Wen, et al., 2007; Pigatto, et al., 2007; Lerch & Bircher, 2004; Koch & Nickolaus, 1996; Nakayama, et al., 1983). With respect to mercury-containing dental amalgam, multiple case reports have documented the rare development of contact or irritant stomatitis in a small number of patients, manifesting as local mucosal reactions due either to allergic or irritant effects. Allergic mucosal reactions to mercury are characteristically erythematous, patchy, pruritic or burning, potentially erosive, and localized to the buccal or lateral glossal mucosal surfaces. However, more common than these responses are lichenoid mucosal reactions that arise in close proximity to dental amalgam prostheses and may be indistinguishable from more distal oral lichen planus or leukoplakia lesions (reviewed in McCullough, et al., 2008; Ditrichova, et al., 2007; Segura-Egea & Bullon-Fernandez, 2004; Wong & Freeman, 2003; Scalf, et al., 2001; Carnisa, et al., 1999; Tosti, et al., 1997; Koch & Bahmer, 1995; Ostman, et al., 1994; Jameson, et al., 1990; Lind, et al., 1986). These reactions tend to be superficial, non-ulcerated and non-friable reticular lesions that are whitish-grey in

color. Such reactions may not represent true allergic responses in the purest sense, as they may not result from immunologic hypersensitivity mechanisms (Bolewska & Reibel, 1989). Rather, these reactions may reflect the irritant nature of mercury in a small number of individuals who are considered to be mercury sensitive, although the precise pathologic mechanism of such reactions is unknown.

Although mercury was first documented as a contact sensitizer in the late nineteenth century and mercury-induced stomatitis has been described in the medical literature for over 75 years (reviewed in Mackert, 1991), there have been few reliable prevalence estimates of immunologic hypersensitivity or idiosyncratic sensitivity to mercury in the general population, with rates typically cited between 1-5% (Swartzendruber, 1993; reviewed in Holmstrup, 1991; reviewed in Mackert, 1991; von Mayenburg, et al., 1991; reviewed in Bolewska, et al., 1990; Finne, et al., 1982). However, as discussed in detail in the response to Question #4, these population estimates have largely been based on the use of cutaneous allergy patch testing to define hypersensitivity in unselected groups of healthy control patients. Given the absence of long-term prospective studies of mercury-exposed versus non-exposed individuals sampled from the general population, these estimates have been derived from positive results generated by non-standardized patch testing utilizing a variety of mercury-containing compounds, rather than from clinically documented allergic manifestations with a confirmed causal relationship to mercury. In turn, the prevalence of clinically relevant mercury allergy in the general population is likely to be far lower, based on the overall incidence of allergic manifestations in the general population (reviewed in Mackert, 1991). For example, a double-blind study conducted by the North American Contact Dermatitis Group found that 3% of 660 patients patch tested with 1% ammoniated mercury reacted positively, although at the time of testing, only 20% of this positive group demonstrated either a history or current signs of skin disease that could be reasonably attributed to mercury hypersensitivity (Storrs, et al., 1989), suggesting that only 0.6% of this sample could be considered to have confirmed mercury allergy. Moreover, as this study was conducted on patients suspected of contact dermatitis who presented for clinical evaluation, these rates likely overestimate the propensity for true mercury allergy in the general population.

Using similar testing approaches, prevalence rates of mercury hypersensitivity have been shown to be consistently higher in patients with oral lichen planus or lichenoid reactions of the oral mucosa, particularly if associated with adjacent dental amalgam exposures (Bolewska, et al., 1990). Nonetheless, these estimates vary widely in the literature, ranging from 6-79% in this subset of patients, as response rates are variably reported either collectively or individually with respect to a wide array of mercury-containing compounds (reviewed in Bains, et al., 2008; Khamaysi, et al., 2006; Vamnes, et al., 2004; reviewed in Garner, 2004; Thornhill, et al., 2003; Wong & Freeman, 2003; Kanerva et al., 2001; Scalf, et al., 2001; Koch & Bahmer, 1999; Laine, et al., 1997; Gebhardt & Geier, 1996; Ostman, et al., 1994; reviewed in Holmstrup, 1992; Laine, et al., 1992; Nordlind & Liden, 1992; reviewed in Ziff, 1992; reviewed in Mackert, 1991; Skoglund & Egelrud, 1991; James, et al., 1987; Lundström, 1984; Mobacken, et al., 1984; Finne, et al., 1982). Similarly, sensitivity to one or more forms of mercury has been variably estimated at 3-21% in patients with diagnosed or suspected contact dermatitis (Seidenari, et al., 2005; Vozmediano & Hita, 2005; Heine, et al., 2004; Wöhrl, et al., 2003; Lee, et al., 2001; Manzini, et al., 1998; Brasch & Geier, 1997), although in some studies, only half of these reactions were

considered to be clinically relevant, based on history and physical examination (Vozmediano & Hita, 2005).

2) How does mercury allergy differ from mercury sensitivity or mercury poisoning/toxicity?

Division Response:
Mercury allergy connotes a specific pathophysiologic process in which a sensitized individual with a predisposition to mercury hypersensitivity develops an immunologic reaction upon re-exposure to mercury-containing compounds. Such reactions may be in response to elemental mercury or various small molecular weight forms (inorganic, organic, or salt formulations) that act as haptens and form allergenic complexes with host carrier proteins. These reactions are limited to a small number of individuals with a predisposition for mercury allergy but for whom risk factors are, as yet, unrecognized. While some investigators refers to this small segment of the population as being sensitive to mercury, "mercury sensitivity" is a general and imprecise umbrella term that refers to the propensity of an individual to develop either hypersensitivity to mercury or an otherwise idiosyncratic immunologic or non-immunologic adverse reaction to non-toxic and non-irritating levels of mercury exposure, which would not be expected to produce signs or symptoms in the general population. In contrast, mercury poisoning/toxicity refers to the pathologic processes that lead to the cellular dysfunction and tissue damage associated with exposure to sufficiently high levels of mercury, including well-described neurological syndromes and gestational developmental defects (Brownawell, et al., 2005; Kazantzis, 2002; Vahter, et al., 2002; Eley, 1997; Mackert & Berglund, 1997; Munksgaard, 1992; Ziff, 1992; Holmstrup, 1991; von Mayenburg, et al., 1991). Such toxicities would be expected to develop in any individual, given the ability of mercury to disrupt normal cellular processes at high enough levels. Thus, mercury poisoning and toxic reactions are predictable and would not be considered idiosyncratic or related to an underlying allergy. Thus, a pre-existent state of mercury sensitivity would not be required to develop a toxic reaction or poisoning from mercury. Despite these semantic differences, however, localized cutaneous and mucosal reactions to mercury may manifest similarly, whether allergic, irritant, or toxic in origin (Tosti, et al., 1997). Moreover, histologic biopsy findings of these types of cutaneous and mucosal lesions are variable, with no clear relationship to these different etiologies (Carnisa, et al., 1999; Koch & Bahmer, 1999; Bratel, et al., 1998; Ostman, et al., 1994; Bolewska & Reibel, 1989; Hietanen, et al., 1987), although limited immunohistochemistry data have indicated a preponderance of antigen-presenting cells in amalgam-associated lichenoid lesions of allergic patients (Konttinen, et al., 1999).

3) Can the exposures from dental amalgam lead to mercury allergy?

Division Response:
Methods of measuring and estimating the release of inorganic mercury vapor and particulate matter from dental amalgam, which may be comprised of up to 44-66% elemental mercury, are controversial (Brownawell, et al., 2005; reviewed in Swartzendruber, 1993; reviewed in Mackert, 1991). Values for both baseline and induced (e.g., stimulated by chewing; increased with amalgam corrosion) mercury release from *in situ* dental compounds vary widely, according to the current literature (reviewed in Mackert & Berglund, 1997; Ziff, 1993; von Mayenburg, et al.,

1991; reviewed in Brune, 1986). Regardless of the precise amounts of mercury released from these sources and subsequent absorption rates, mercury levels in saliva, urine, and blood positively correlate with the presence and number of mercury-containing dental amalgam prostheses (Prochazkova, et al., 2006; Vamnes, et al., 2004; Bergdahl, et al., 1998; Herrström, et al., 1997; Olstad, et al., 1987). However, systematic comparative studies of amalgam-exposed versus unexposed individuals have not demonstrated an association between dental amalgam and mercury poisoning/toxicity (reviewed in Eley, 1997). In contrast, an association between dental amalgam and mercury allergy is better established. As discussed above, the pathophysiology of an allergic response involves the initial sensitization of a susceptible individual to an allergen, followed by re-exposure to that same allergen, which triggers an allergic immune response. Thus, mercury exposure from dental amalgam may cause sensitization to mercury in a limited number of individuals (Kanerva, et al., 1993; Feuerman, 1975). Likewise, exposure to mercury in dental amalgam may trigger an allergic response in a hypersensitive individual previously sensitized to mercury (Munksgaard, 1992). Of note, however, the observed rates of these reactions in clinical practice is low, as discussed in the response to Question #1, with only a small fraction of patients displaying documented immunologic hypersensitivity to mercury and an even smaller percentage than this manifesting true IgE-mediated immediate hypersensitivity.

Individual case reports and limited case series in the literature describe the resolution of clinical signs and symptoms following the removal of sources of mercury exposure, such as dental amalgams (Laeijendecker, et al., 2004; Thornhill, et al., 2003; Wong & Freeman, 2003; Scalf, et al., 2001; Koch and Bahmer, 1999; von Mayenburg, et al., 1996; Gebhardt & Geier, 1996; Ibbotson, et al., 1996; Koch & Bahmer, 1995; Pang & Freeman, 1995; Lind, et al., 1986). While long-term follow-up would be required to confirm that these symptoms do not re-emerge following the removal of dental amalgam or other sources of mercury exposure (Henriksson, et al., 1995; Laine, et al., 1992), such amelioration suggests a role for mercury as a causative agent. However, larger comparative studies have not demonstrated a consistent benefit from the removal of dental amalgam prostheses in the relief of self-reported symptoms attributed to mercury allergy. Re-emergence of the reaction in question following re-introduction of the potentially offending agent may confirm the causative nature of the allergen (Holmstrup, 1991). However, given that allergic responses to mercury are often delayed by days to weeks after exposure, this is typically impractical for diagnostic purposes. In addition, ethical considerations may preclude the intentional re-introduction of mercury exposure to test this hypothesis.

4) How is mercury allergy diagnosed and can a predisposition to mercury allergy be determined?

Division Response:

Mercury exposure has been implicated in a whole host of non-specific somatic complaints, despite a lack of objective confirmation (Gottwald, et al., 2002; Langworth, et al., 2002; Gottwald, et al., 2001; Langworth, et al., 1993; reviewed in Mackert, 1991; Meurman, et al., 1990). However, mercury allergy should be suspected only if a thorough medical history including occupational and home exposures implicates one or more sources of mercury exposure (e.g., dental amalgam restorations, broken liquid mercury thermometers, mercury-containing cosmetics) as having a plausible temporal association with a typical allergic clinical

manifestation, such as contact dermatitis or IgE-mediated immediate hypersensitivity reactions, as described above. This information can only provide a potential explanation for an allergic reaction, however, and by itself cannot confirm mercury allergy.

At present, no gold standard diagnostic test exists to confirm mercury allergy, and no laboratory test has been developed to screen for a predisposition to mercury allergy, although researchers have attempted to develop both *in vivo* and *in vitro* diagnostic tests based on the presumed immunopathogenesis of mercury allergy. As the majority of mercury hypersensitivity reactions are thought to occur due to cell-mediated processes involving allergen-specific T cells, rather than allergen-specific IgE and mast cells, diagnostic tests have sought to characterize the ability of the lymphocyte compartment to react to mercury or its derivatives. Several studies have utilized *in vitro* lymphocyte stimulation assays (also called lymphocyte transformation assays) in which peripheral blood mononuclear cells (primarily lymphocytes and monocytes) from individuals suspected of mercury allergy are exposed *ex vivo* to various forms of mercury (e.g., thimerosal, dental amalgam, mercury salts) in order to induce cellular proliferation among antigen-specific memory cells as quantified by radioactive DNA labeling with tritiated thymidine (reviewed in Bains, et al., 2008; Valentine-Thon, et al., 2006; Venclikova, et al., 2006). Although such assays have gained acceptance in some European countries and have been cited by some researchers as an objective diagnostic tool (Valentine-Thon & Schiwara, 2003; Stejskal, et al., 1996), questions persist as to their predictive and diagnostic value, particularly given the potential for some forms of mercury to induce non-specific cellular proliferation (Cederbrant, et al., 1999). At present, lymphocyte stimulation assays are not accepted in the United States as a standardized or validated diagnostic test by the American Academy of Asthma, Allergy, and Immunology (AAAAI) or the American College of Asthma, Allergy, and Immunology (ACAAI), two major professional societies comprised of allergists and immunologists. Thus, rather than predicting mercury allergy, allergen-specific lymphocyte proliferation assays are more typically used for research purposes to indicate past exposure to mercury (Henderson, et al., 2001; Cederbrant, et al., 2000; Laine, et al., 1997).

Delayed-type hypersensitivity patch testing has gained wider acceptance in the United States as an *in vivo* diagnostic tool for allergic contact dermatitis, including mercury hypersensitivity (Holmstrup, 1991). In this test, known concentrations of potential allergens are suspended in a non-irritating vehicle, such as petrolatum, and are then applied directly to the skin of the back for up to 96 hours. Localized epicutaneous reactions are then observed periodically throughout this period for evidence of various gradations of delayed-type contact hypersensitivity reactions, e.g., erythema, induration, scaling, and vesicle formation. Observations made within several hours of allergen placement are also recorded to rule-out immediate hypersensitivity reactions (e.g., erythema and urticaria), which would be expected to occur much sooner than classic delayed-type hypersensitivity responses. Negative controls with vehicle only are also applied to rule-out non-specific skin reactions. The allergen patch test is considered by many experts in the fields of dermatology and allergy and immunology to be the gold standard diagnostic test for contact dermatitis and other forms of delayed-type cell-mediated hypersensitivity. However, despite the publication of allergy skin testing guidelines by multiple professional societies and the commercial availability of standardized allergen patch testing panels (Holmstrup, 1991), wide variability still remains in the execution of these tests, as related to the choice of mercury-containing compounds and other dental materials, as well as in the subjective interpretation of

their results (Muris & Feilzer, 2006; Koch & Bahmer, 1999; Nakada, et al., 1997; Handley, et al., 1993). In particular, individually applied allergens at non-standardized concentrations may elicit false positive irritant skin reactions, rather than true cell-mediated immunologic responses (reviewed in Bains, et al., 2008; Carnisa, et al., 1999; Pirker, et al., 1993; Holmstrup, 1991; reviewed in Mackert, 1991; von Mayenburg, et al., 1991; Namikoshi, et al., 1990; Hietanen, et al., 1987). Similar to allergic skin prick tests, positive reactions on cutaneous patch tests are non-specific and are not always associated with an underlying clinical manifestation of allergy. Moreover, the sensitivity and predictive value of non-standardized compounds used in skin patch testing has not been established through rigorous evaluation.

In general, allergen exposure levels must be several times higher (5-12 fold) in order to elicit oral mucosal responses, as compared to cutaneous reactions (Holmstrup, 1991), possibly due to the decreased concentration of T cells and antigen-presenting Langerhan's cells in the oral mucosa. In addition, cutaneous allergic reactions may not involve the same host protein-hapten complexes as mucosal allergic reactions, thus leading to non-informative results on cutaneous patch testing. For example, one study demonstrated a patch test positivity rate of 2% to dental amalgam but further showed that only 37% of these patients patch tested positive to mercury (von Mayenburg et al., 1991). Another study indicated that only 4% of patients who were patch test positive to thimerosal subsequently developed reactions to intramuscular challenge with thimerosal-containing vaccines (Audicana, et al., 2002). Moreover, thimerosal positivity on skin patch testing does not reliably correlate with patch test reactivity to inorganic mercury (Santucci, et al., 1998). Therefore, as a diagnostic tool for mercury allergy, cutaneous patch testing can only offer supportive evidence of an underlying hypersensitivity to mercury compounds and cannot be used to definitely diagnose mercury allergy. Furthermore, the utility of using cutaneous patch testing as a screen to identify a predisposition to mercury allergy has not been validated. In fact, although skin patch tests are often cited as such in the literature, at present there are no validated diagnostic tests available to screen patients for mercury allergy prior to known exposures. Therefore, in clinical practice, a cutaneous patch test to multiple forms of mercury, including the formulation expected of being the causative agent (e.g., dental amalgam at various concentrations) is most appropriately performed after the suspicion of mercury allergy has been raised based on a thorough medical history and clinical examination, with a plausible temporal relationship to a known mercury exposure (Ditrichova, et al., 2007). In these instances, a negative patch test result is most useful in ruling-out mercury contact hypersensitivity, as insufficient evidence exists for universally recommending the removal of dental amalgam prostheses in the setting of a positive patch test result, as contact lesions within the oral mucosa may be self-limited and resolve without intervention in 1-3 weeks (reviewed in Bains, et al., 2008). Thus, the decision to partially or completely remove dental amalgams following a positive mercury patch test result must be individualized for each patient (Smart, et al., 1995).

5) Are there genetic predispositions to mercury allergy?

Division Response:
Studies linking mercury allergy to genetic predispositions in humans are extremely limited. Evidence does not exist to support a clear association between any particular gene allele or HLA haplotype, although several hypothesis-generating reports are documented in the literature that

suggest an association between HLA haplotype and one or more forms of mercury sensitization. These include non-statistically significant preponderances of the following alleles in patients with reported mercury intolerance: HLA-DR6 in a small sample of mercury-sensitized (n=20) versus non-sensitized (n=22) Japanese medical students (Sato, et al., 1996); HLA-B37, HLA-B47, and HLA-DR4 in a small sample (n=25) of Czech patients with intolerance of dental amalgam and metal alloys, as compared to population data from a Czech bone marrow registry (Prochazkova, et al., 2000); and shared HLA haplotypes (DRB1*0701; DQA1*0201; DQB1*0202/DRB1*11; DQA1*0505; DQB1*0301) in two unrelated Italian patients with burning oral manifestations and positive skin patch testing to mercury (Pigatto, et al., 2007). In addition, a statistically significant preponderance of homozygous deletion mutations for the glutathione S-transferase M1 and T1 (GSTT1 and GSTM1) alleles were observed in a group of Central European adults (n=91) who were patch test-positive to thimerosal, as compared to healthy controls (n=169), potentially suggesting a functional implication for defects in glutathione-dependent metabolism in individuals hypersensitive to mercury (Westphal, et al., 2000). Another study has suggested the activity of superoxide dismutase, which is involved in oxidative metabolism, may be higher in patients who self-report themselves as intolerant to mercury, based on subjective psychosomatic complaints (Marcusson, et al., 2000). However, despite these findings, there is currently insufficient evidence in the literature to support any known genetic associations with mercury allergy. Thus, genetic screening for mercury allergy is currently unavailable.

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